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Different Levels of Platelet Activation in Normal Pregnancy and Pregnancy-induced Hypertension (PIH)

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We examined the effects of pregnancy and pregnancy-induced hypertension (PIH) on platelet activation. Thirty-six women with PIH (blood pressure >140/90 mm Hg after two consecutive measurements after the 24th weeks of gestation) without proteinuria, fifty-six normotensive pregnant women, and fifty non-pregnant women were studied. WBC, RBC, platelet related variables, including mean platelet component (MPC), mean platelet volume (MPV) and platelet component distribution width (PCDW) were determined for this study. MPC levels were significantly lower in women with PIH compared with normotensive pregnant women and non-pregnant women ($P<0.05$). MPC levels were inversely correlated with PIH ($r=-0.49$, $P<0.001$), systolic BP ($r=-0.22$, $P<0.01$), diastolic BP ($r=-0.17$, $P<0.05$), WBC ($r=-0.30$, $P<0.001$), MPV ($r=-0.41$, $P<0.001$), and PCDW ($r=-0.68$, $P<0.001$), and positively correlated with RBC ($r=0.32$, $P<0.001$), platelet count ($r=0.21$, $P<0.05$), and mean platelet mass (MPM) ($r=0.18$, $P<0.05$). MPC levels were found to be an independent factor associated with PIH and PCDW ($P<0.01$) after adjustments were made for potential confounding factors such as gestational age, systolic blood pressure, diastolic blood pressure, WBC, RBC, Platelet count, and PCDW. In conclusion, MPC levels were significantly lower in women with PIH, and MPC levels were found to be an independent factor associated with PIH and PCDW. Therefore, platelet activation is suggested as a useful predictor for patients with PIH.

Key Words: Pregnant, Hypertension, Platelet activation, Mean platelet component

INTRODUCTION

Pregnant women with hypertension remain at risk for severe complication such as abruption placenta, cerebrovascular accident, end-organ failure and disseminated intravascular coagulation (Sibai et al., 1986; Perry et al., 1992; Sibai, 1992; Nisell et al., 1995). As well as, the fetus is at risk for intrauterine growth retardation, prematurity and intrauterine death (Sibai et al., 1986; Peek et al., 1995). Although the basic mechanism and pathophysiology is still unclear, there has been interest in the role of platelets in the pathogenesis of pregnancy-induced hypertension (PIH). Platelet activation has been demonstrated to be present in hypertension (Nityanand et al., 1993; Minuz et al., 1994). Possible explanations for the increased platelet activation are an intrinsic change in platelet responsiveness or increased consumption and turnover within the microvasculature secondary to hypertensive vasospasm (Socol et al., 1985).

The density of platelets decreases upon activation, due to the release of alpha granules and dense granules (Corash et al., 1977). Mean platelet component (MPC) values have been shown to have a strong inverse correlation with the CD62P expression as a measure of platelet activation, and P-selectin secreted by platelet membrane (Chapman et al., 2003). Also platelet activation related to the mean platelet volume (MPV) (Ahmed et al., 1993), which represents platelet size, and the platelet component distribution width (PCDW) (Mezzano et al., 1981; Lim et al., 2002). With recent advances in automatic blood cell counting, a fast and accurate determination of platelet count and volume can be made.

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Although there is evidence in the involvement of platelet activation in several disorders, the concept remains relatively undeveloped especially in PIH. To examine the effects of pregnancy and pregnancy-induced hypertension on platelet activation we conducted a cross-sectional study of women with PIH, who were compared with normotensive pregnant women of comparable gestation, and normal non-pregnant women.

MATERIALS AND METHODS

We recruited thirty-six women with PIH (blood pressure >140/90 mm Hg after two consecutive measurements after the 24th weeks of gestation) without proteinuria, fifty-six normotensive pregnancy women, and fifty non-pregnant women. Body weight was measured to the nearest 0.1 kg on an electronic scale. Subjects were weighed in light clothing and without shoes.

For the evaluation of platelet activation, we collected 5 ml of blood in a vacuum tube containing EDTA as an anti-coagulant. WBC, RBC, platelet related variables, including MPC, MPV and PCDW were determined within 1 hour after blood collection using the ADVIA 120 automated hematology analyzer (Bayer, Tarrytown, NY, USA). Before being used for the examination, the instrument was calibrated using the Bayer SET point calibrator and the Bayer OPTI-point (Bayer, Tarrytown, NY, USA).

Data are presented as means ± SD. Significance of mean differences among three groups was determined with one-way analysis of variance (ANOVA) and post hoc analyses (SPSS, version 12, Chicago, IL, USA). Post hoc analyses were made with Tukey's multiple comparisons. Pearson correlation analyses were used to determine the relationship between MPC and various parameters. Multiple regression analyses, adjusted for gestational age, systolic BP, diastolic BP, WBC, RBC, Platelet count, PCDW were used to determine the variables related to platelet activation. Statistical significance of mean differences was set at α=0.05.

RESULTS

The clinical characteristics of subjects and platelet activation parameters are shown in Table 1. Women with PIH were significantly higher systolic BP, diastolic BP, and WBC. The pregnant groups had lower platelet count than non-pregnant group. MPV and PCDW were significantly different among three groups studied (Table 1). MPC levels were significantly lower in women with PIH compared with

Table 1. Clinical characteristics of subjects, and platelet activation parameters

Variables	PIH[a] (N=36)	Normotensive pregnant women (N=56)	Non-pregnant women (N=50)
Age (years)	32.3±3.1	32.5±4.1*	30.1±5.5
Gestational variables			
Gestational age (weeks)	31.3±4.3‡	28.1±4.1	-
Weight gain (kg)	9.2±4.5‡	7.2±3.4	-
Blood pressure			
Systolic (mm Hg)	150.4±1.0†§	108.9±10.1	111.4±11.2
Diastolic (mm Hg)	94.8±7.8†§	63.5±8.7	67.4±10.5
Hematologic variables			
WBC (10^3/μl)	9.7±2.2†	8.8±1.9†	5.3±1.4
RBC (10^6/μl)	3.7±0.7†	3.6±0.3†	4.3±0.2
Platelet variables			
Platelet count (10^3/μl)	223.5±52.3†	220.1±48.0†	262.5±64.8
PDW[b] (%)	62.4±6.1†§	56.4±6.4	55.5±6.4
MPV[c] (fl)	8.59±1.0†§	7.97±0.8*	7.58±0.7
PCDW[d] (pg)	5.92±1.0*‡	6.31±0.7†	5.5±0.4
MPM[e]	2.1±0.2*§	1.9±0.3	2.0±0.1

Values are means ± SD. *P<0.05; †P<0.01 versus Non-pregnant women; ‡P<0.05; §P<0.01 versus Normotensive pregnant women.
[a]Pregnancy-induced hypertension; [b]platelet distribution width; [c]mean platelet volume; [d]platelet component distribution width; [e]mean platelet mass

Table 2. Correlations between MPC[a] levels and various parameters

Variables	MPC	
	r	*P*-value
Age (Years)	-0.12	0.16
Case (PIH)[b]	-0.49	<0.001
Gestational variables		
Gestational age (Weeks)	0.006	0.96
Weight gain (Kg)	0.10	0.41
Blood pressure		
Systolic (mm Hg)	-0.22	<0.01
Diastolic (mm Hg)	-0.17	<0.05
Hematologic variables		
WBC (10^3/μl)	-0.30	<0.001
RBC (10^6/μl)	0.32	<0.001
Platelet variables		
Platelet count (10^3/μl)	0.21	<0.05
PDW[c] (%)	0.05	0.58
MPV[d] (fl)	-0.41	<0.001
PCDW[e](pg)	-0.68	<0.001
MPM[f] (fl)	0.18	<0.05

Coefficients (*r*) and *P*-values are calculated by the Pearson correlation model.
[a] Mean platelet component; [b] pregnancy-induced hypertension,
[c] platelet distribution width; [d] mean platelet volume;
[e] platelet component distribution width; [f] mean platelet mass

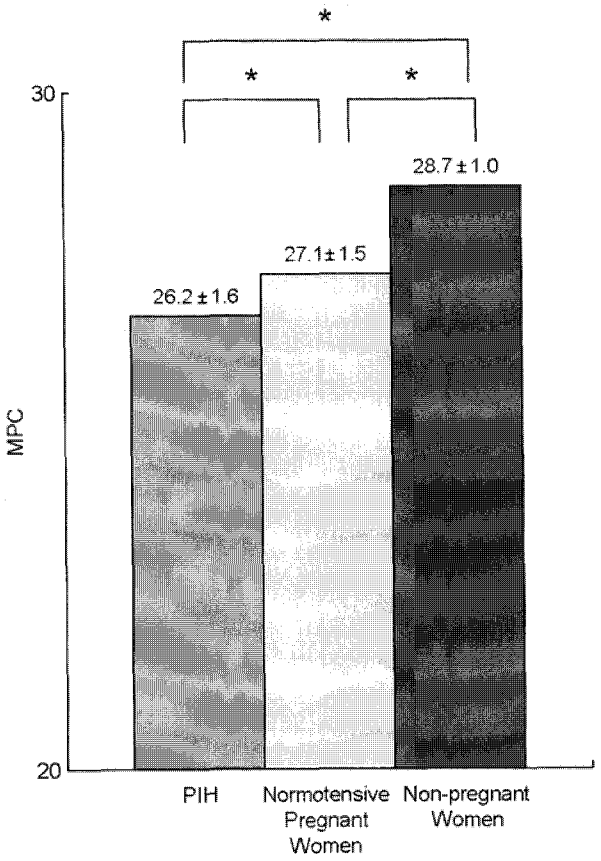

Fig. 1. Mean platelet component (MPC) levels in three subjects. MPC levels were significantly lower in women with pregnancy-induced hypertension (PIH) compared to normotensive pregnant women, and non-pregnant women. *P<0.001.

normotensive pregnant women, and non-pregnant women (P<0.05, Fig. 1). MPC levels were inversely correlated with case (PIH) (r=-0.49, P<0.001), systolic BP (r=-0.22, P< 0.01), diastolic BP (r=-0.17, P<0.05), WBC (r=-0.30, P< 0.001), MPV (r=-0.41, P<0.001), and PCDW (r=-0.68, P< 0.001), and positively correlated with RBC (r=0.32, P< 0.001), platelet count (r=0.21, P<0.05), and mean platelet mass (MPM) (r=0.18, P<0.05) (Table 2). MPC levels were found to be an independent factor associated with PIH and PCDW (P<0.01, respectively) after adjustments were made for potential confounding factors such as gestational age, systolic BP, diastolic BP, WBC, RBC, Platelet count, PCDW (Table 3).

Table 3. Association between several factors and mean platelet component by multiple analyses[a]

Variables	β	SE	*P*-value
Case (PIH)[b]	-0.409	1.80	<0.001
Gestational age	-0.038	0.03	0.68
Systolic BP	-0.062	0.02	0.82
Diastolic BP	0.023	0.02	0.93
WBC	0.060	0.06	0.48
RBC	-0.037	0.24	0.65
Platelet	0.12	0.002	0.14
PCDW[c]	-0.70	0.15	<0.001

[a]: Calculated by multiple regression model using MPC as the dependent variable (R^2=0.52, F-value 10.6, P<0.01);
[b]: pregnancy-induced hypertension;
[c]: platelet component distribution width

DISCUSSION

The results of the present investigation demonstrated that MPC levels were significantly decreased in PIH as compared to normotensive pregnant women, and non-pregnant women, suggesting that platelet activation might occur in PIH. In addition, our findings on the association between MPC and PIH were also consistent with those of previous studies, including the study on pre-eclampsia (Socol et al., 1985; Janes et al., 1994; Konijnenberg et al., 1997), and on PIH (Karalis et al., 2005). Morrison et al (1985) found a

marked increase in platelet reactivities throughout pregnancy, both in normotensives and in patients with underlying essential hypertension. In contrast, Harlow et al (2002) found that platelet activation increased in pre-eclampsia but not in other forms of hypertension in pregnancy. In this study, other platelet activation variables, such as MPV and PCDW, were significantly increased in PIH whereas Karalis et al (2005) did not show any significant differences in platelet morphology features (MPM, MPV) among groups (PIH, normotensive pregnant women, and non-pregnant women).

We also found that MPC levels were significantly correlated with systolic BP and diastolic BP, suggesting that platelet activation may occur in hypertension in a blood pressure-dependent manner. These data are in line with other studies, showing that CD62 was significantly correlated with systolic BP and diastolic BP in hypertension patients (Richard et al., 2006), and that pP-selectin was correlated with diastolic BP in PIH (Karalis et al., 2005). In this study, the pregnant groups (PIH and normotensive pregnant women) had lower platelet count than non-pregnant women. These results suggest that increased platelet activation should lead to platelet exhaustion and consumption and consequent lowering of the platelet count.

The limitations of this investigation were that a limited cross-sectional population was studied, and we have no direct evidence for a cause-effect interaction. Overall, the role of increasing platelet activation measured as MPC levels in the screening and classification of pregnancy related hypertensive disorder is weakly understood, and further enlarged study is needed to clarify this phenomenon. The new platelet parameter MPC may be used to detect resting or activated platelets. The measurement of MPC does not require specimen preparation, platelet activation-specific receptors, or activation-specific receptor labels. (Macey et al., 1999; Chapman et al., 2003) and easier and more time-saving than previous methods, screening large populations may be more feasible.

In conclusion, MPC levels were significantly lower in women with PIH, and MPC levels were found to be an independent factor associated with PIH and PCDW. Therefore, platelet activation is suggested as a useful predictor for patients with PIH.

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